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Disease-a-Month

Brucellosis

ABRAHAM I. BRAUDE

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Brucellosis

ABRAHAM I. BRAUDE

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Abraham S. Braude

is Professor of Medicine at the University of Texas Southwestern Medical School and Director of the Bacteriology Laboratory, Parkland Memorial Hospital, Dallas, Texas. Dr. Braude received his M.D. degree from Rush Medical College of the University of Chicago. During the years 1946-1950 he engaged in research on brucellosis at the University of Minnesota as a member of the group directed by Wesley W. Spink. At present, he is conducting investigation in basic clinical problems dealing with immunology and infection.

IT IS SOMETIMES forgotten that brucellosis is the name given not to one, but to a group of 3 related diseases in which infection is produced by one of 3 organisms: Brucella abortus, Brucella suis or Brucella melitensis. The similarity among the 3 diseases is so great that they can seldom be distinguished on a clinical basis, but close attention to the epidemiologic history and careful examination of the responsible bacteria will allow an exact diagnosis. Before considering the characteristics of each of the 3 types of brucellosis it is necessary to examine their common features.

COMMON FEATURES OF THE THREE TYPES OF BRUCELLOSIS

Mode of Infection

Human brucellosis is acquired from animals. Because the disease is widespread in all common domestic animals—including cattle, swine, goats, sheep and even horses—brucellosis has become the most important human illness among those transmitted from animals. The intimate contact of farmers, butchers, packinghouse workers and dairy personnel with these animals

and the dissemination of the infection through dairy products or meat to consumers provide greater opportunity for spread to human beings than that of any other infection acquired from domestic animals. As a consequence human brucellosis is more widespread than trichinosis, ornithosis, salmonellosis, leptospirosis and anthrax. The highly invasive properties of all 3 species of Brucella contribute to their dissemination by enabling them to penetrate both skin and mucous membranes of unsuspecting victims who fail to recognize the hazard of exposure because the infected animals appear well. This remarkable ability to establish sustained infections of low pathogenicity for animals but high communicability to man is perhaps the most important property possessed in common by all 3 species of Brucella. Human infections, on the other hand, are almost never communicable even in the presence of severe illness (71).

Pathogenesis

The exact route taken by Brucella organisms after entering the skin or mouth is not known. Although the bowel is protected from Brucella organisms by the lethal action of gastric juice, the mucous membranes of the mouth are vulnerable to invasion and offer a likely portal of entry for many of the infections which follow consumption of dairy products (30). No discernible reaction occurs at the point of penetration in susceptible persons and the bacteria are dispersed through the circulation with apparent localization in tissues rich in reticuloendothelial elements. The evidence in favor of the reticuloendothelial localization of Brucella organisms is derived mainly from the observation that the basic lesion, the granuloma, is present in large numbers in the liver, spleen, bone marrow and lymph nodes of patients with brucellosis (74, 76, 90). While it is true that the organisms cannot usually be demonstrated by culture or direct microscopic examination in tissues containing these granulomas, there is convincing experimental evidence that the granulomas originate from the cells which attack the invading Brucella organisms (9, 10). Within several hours after living Brucella cells are inoculated intraperitoneally in mice, for example, groups of polymorphonuclears containing Brucellae

collect in the sinusoids of the liver in focal aggregates which also include parasitized Kupffer cells. The polymorphonuclears and their bacterial contents are soon ingested and replaced by Kupffer cells, and small groups of the mononuclear macrophages filled with intracellular bacteria accumulate within the sinusoids. As these mononuclear aggregates increase in size, two noteworthy events occur: (1) the cells take on the characteristics of epithelioid cells and (2) most of the intracellular bacteria are destroyed. Within a week these collections of epithelioid cells are recognized as fully developed granulomas. Because the granulomas remain in the tissues only as long as infection is demonstrable, it is clear that Brucella organisms are required for their perpetuation just as they are for initiating their development.

The success of the granuloma in defending the host from Brucella infection is suggested by the low incidence of clinical disease in persons who give evidence of tissue invasion by Brucella organisms. Thus in endemic areas clinical brucellosis may be present in less than 1% of persons who exhibit hypersensitivity to Brucella antigens (81). The immunologic importance of the granulomas is also indicated by their universal existence in hepatic tissue or marrow removed by needle biopsy from persons with sublethal infections and their consistent absence in patients whose resistance is so low that death occurs (74, 87, 88, 90). The granuloma, however, by no means provides a perfect cellular defense against Brucella. In fact, there is reason to believe that the mononuclear cells of the granuloma may perpetuate the infection by harboring intracellular organisms and protecting them from antibodies and antibiotic drugs (77).

Aside from the granuloma, most patients with brucellosis present no morphologic evidence of infection on microscopic examination of their tissues, and even this lesion is usually absent in fatal cases (87, 88). The granulomas are often numerous in the liver, spleen or marrow, but do not usually seem to impair the function of the affected organs (74). Because the pathologic findings are thus inadequate to account for the clinical symptoms, it is obvious that the bacteria can induce physiologic disturbances in the absence of observable tissue injury. Chemical fractionation of the Brucella cell has yielded two fractions which can reproduce many of the clinical symptoms of brucellosis on

injection into the tissues. One of these, a protein derivative, is harmless when injected into normal persons but elicits high fever, chills, sweats, muscular aches, headache, malaise, nausea and weakness in persons who have had Brucella infection (32). The lipopolysaccharide fraction can produce these symptoms in normal persons in the absence of previous Brucella infection, but sensitivity to this substance is also increased in patients with brucellosis (2, 62). It has been suggested, therefore, that this sensitivity to the toxic effects of Brucella fractions is responsible for the severe systemic symptoms during active clinical brucellosis. As little as 0.001 mg. of the lipopolysaccharide will evoke a severe systemic response on intravenous injection in patients with brucellosis (2).

This hypersensitivity to bacterial products during infection is not peculiar to brucellosis; it was first observed by Koch in tuberculosis and has since been studied in many other types of infection (25, 29, 47, 48). Nor are the toxic properties of the lipopolysaccharide unique to that derived from Brucella cells. This substance is found in the cell walls of all Gram-negative (but not Gram-positive) bacteria and is designated "endotoxin." The lipopolysaccharides from different bacterial species are potentially lethal poisons which are similar chemically and produce the same physiologic reactions when given in equivalent sublethal amounts (7). It is probably for this reason that the clinical manifestations of each type of brucellosis resemble not only each other, but also those of infections due to such diverse organisms as Escherichia coli, Salmonella typhosa and Pasteurella tularensis.

A remarkable property of these lipopolysaccharides, which might have a bearing on the clinical course of infection, is their capacity to induce a state of resistance or tolerance (6). When they are injected repeatedly in the same dose at daily intervals, for example, the subject sustains progressively less fever or systemic complaints. After a lapse of such injections, however, the tolerance wanes and susceptibility to the systemic effects of endotoxin is restored. The relapsing pattern of the disease in some patients with brucellosis brings to mind the waning tolerance observed when exposure to endotoxin is discontinued and suggests that clinical relapse may be related to loss of tolerance to Brucella endotoxin.

Clinical Manifestations

The clinical similarities of the 3 forms of brucellosis are far more striking than their differences. Regardless of the species of Brucella, most patients with brucellosis exhibit a remarkable syndrome characterized by numerous and often severe symptoms but only few objective abnormalities. The predominant symptoms are fever, sweats, weakness and generalized pains. While these lead to pronounced suffering and even incapacitation, the patient often looks surprisingly well. Many infected persons continue at their employment because the onset of symptoms can be so insidious that the change from health to sickness is not distinctly recognized (78, 84). Eventually, however, most patients quit their work when they discover that they feel better while inactive. This symptomatic improvement associated with rest is one of the outstanding features of brucellosis and must be kept in mind not only as an important diagnostic point but also from the standpoint of treatment. Before the discovery of specific chemotherapy, rest in bed was the only available treatment and often led to a decline of fever, relief from generalized pains and gain in strength. Patients accordingly become so dependent on physical rest as the only means of securing relief that after the febrile phase of the illness is over they have great difficulty in going back to work. Convalescence is, therefore, characteristically long because of the slow return of strength. In all forms of brucellosis the last symptom to disappear is weakness and its persistence is largely responsible for the discouragement and sometimes severe emotional depression that occur in patients who cannot pursue their usual and necessary occupations (79).

While most ambulatory patients with active Brucella infection are forced off their feet by the need for rest, a few have no complaints and even continue at hard work despite bacteremia. The relative frequency of such cases is impossible to determine because the patients do not seek medical attention and are discovered only by epidemiologic search of asymptomatic cases in endemic areas or during the rare epidemics of brucellosis. Because the incidence of dermal hypersensitivity to Brucella antigens may range from 10 to 20% in persons who give no history of clinical brucellosis, it is likely that many persons may sustain Brucella infection without symptoms (81).

In the typical patient with brucellosis who complains bitterly of weakness, headache, backache, insomnia, nervousness, sweats and fever, there are frequently no abnormalities on physical examination (18, 26, 35, 79). When physical findings are present they result from enlargement of those organs rich in reticuloendothelial elements. The spleen and lymph nodes are enlarged and palpable in about half of the patients, and the liver in approximately a fifth. Sometimes these enlarged organs are also tender.

Course and Chronicity

Most patients with brucellosis recover in less than a year. In studying the duration of the disease among hospitalized British military and civilian personnel in Malta, for example, Eyre (26) noted that 85% of patients had recovered within 3 months after onset of symptoms. Similarly, in a careful study of patients from whom Br. abortus was isolated in Minnesota, Spink found that disability no longer existed in 80% of patients or more after 1 year (80). Because the patients comprising both studies usually required special hospital care, they were more severely ill than the average patient and the duration of their illness was longer. It is important to realize, therefore, that brucellosis is a self-limited disease which usually terminates in several months. While localizing complications are demonstrable in most patients who remain ill with brucellosis for longer than a year, there are a few patients (especially those in whom the disease is due to Br. melitensis) in whom bacteremia may continue for that period without demonstrable complications. In other cases, complaints of ill health may persist for several years despite negative cultures or absence of complicating processes. These protracted complaints, which persist longer than all objective evidence of active infection, usually resemble those seen in patients with emotional disorders. They undoubtedly represent latent psychoneurotic symptoms which are brought out by the wearing and incapacitating febrile illness in patients who are less stable emotionally than others. It is believed that these symptoms fail to subside after the infection is checked or eliminated and that the patients continue to suffer from neuropsychiatric sequels of brucellosis rather than the direct effects of the living Brucella organisms.

Complaints similar to these are naturally observed frequently in patients who have never had the usual clinical form of brucellosis. In some of these patients, however, a diagnosis of "chronic brucellosis" is made because their symptoms resemble the neurotic complaints which persist after recovery from proved brucellosis (4). In areas in which brucellosis is endemic, cases of so-called "chronic brucellosis" sometimes exhibit positive skin tests to Brucella antigens and even very low titers of blood agglutinins, but the incidence of positive tests is no greater in them than in their healthy, uncomplaining neighbors.

While it is true that in certain well-localized Brucella infections there may be no more laboratory evidence of brucellosis than in the neurotic patients, it is important to recognize that such focal Brucella lesions may not be accompanied by systemic complaints. In a recent report of pulmonary "coin lesions" from which Br. suis was isolated after surgical resection, none of the patients was reported to have clinical symptoms that resembled those described in the alleged cases of "chronic brucellosis" (92). Hence the contention that a hidden focus of Brucella infection could be the basis of such symptoms is not well substantiated by known cases.

It is also important to recognize that 80% of these patients are women, in contrast to bacteriologically proved cases in which males predominate, that they rarely give a history of exposure, and that their symptoms are not amenable to the specific chemotherapy which is so consistently effective in alleviating the complaints of patients from whom Brucella organisms can be recovered (36). One of the most useful points in recognizing these patients and in ruling out brucellosis is the duration of symptoms; most of them give histories of poor health lasting 5 to 20 years.

Complications

Localized infection of bones, joints, endocardium, central nervous system and genitalia are produced by all 3 species of Brucella. The most common of these is spondylitis, but fortunately its outlook is good. The most serious is endocarditis, a disease which had been uniformly fatal until specific chemotherapy came into use. The meningo-encephalitis of brucellosis may also be fatal but

its prognosis is often remarkably favorable when compared with that of the meningitis occurring in other granulomatous diseases such as tuberculosis and certain mycoses.

The following features characterize each of these complications.

SPONDYLITIS.—The granulomatous lesions which are readily found in the marrow of patients with brucellosis are probably the initial stage in the genesis of vertebral abscesses (28, 51). Because osteomyelitis occurs more frequently in the vertebrae than in other bones in brucellosis, it would seem that weight-bearing trauma is a predisposing factor to spinal localization. This possibility appears likely because of the predominant involvement of the lumbodorsal spine, which is the portion most commonly affected in another disease of traumatic origin, namely, osteoarthritis (51). The importance of weight-bearing is also favored by the relative frequency of Brucella arthritis in joints of the lower extremity (79).

The granulomatous process in the cancellous portion of the vertebral body extends through the bony end-plate and destroys the intervertebral disk. Only one intervertebral disk and the two adjoining vertebral bodies are ordinarily involved, while lesions in multiple vertebrae and disks are exceptional. The destroyed portions of bone, cartilage or nucleus pulposus are replaced by a soft granulation tissue which has a tendency to undergo caseation necrosis. These processes may take the form of either well-circumscribed abscesses in the bone or sheets of yellowish soft tissue containing caseous nodules. Although the intervertebral disk is most vulnerable to the destructive granulation tissue, the process may also extend posteriorly through the posterior longitudinal ligament to involve the meninges, or anteriorly into the prevertebral area where large soft-tissue abscesses often develop (51).

Pain is the outstanding clinical evidence of Brucella spondylitis. It is present over the involved area of the spine, but may also radiate along the distribution of those nerves whose roots are compressed in the region of the destroyed intervertebral disk. Much of the sciatica occurring in brucellosis probably results from this type of lesion, although it is possible that the nerve itself becomes infected in other instances. Until evidence of infection is found, the diagnosis of herniated nucleus pulposus is

usually made in patients with Brucella spondylitis because their sciatic involvement produces the same symptoms. Roentgenographic examination of the spine is not always of value in differential diagnosis because disappearance of the intervertebral space may be the only significant change in both conditions (51). In brucellosis of the spine, however, there is a marked tendency for formation of new bone in the area of osteomyelitis and it is evident roentgenographically by the formation of "parrot-beak" exostoses, anterior bony ridges and ossification of the intervertebral disk. These signs of bone repair are also important in differentiating Brucella spondylitis from tuberculous spondylitis, which shows little if any evidence of healing. Tuberculosis of the spine otherwise bears such a close similarity to Brucella spondylitis that the latter condition has been called pseudo-Potts disease (51). The tendency for the infected spine to heal in brucellosis is so great, however, that full clinical recovery may be expected in most cases without surgical intervention (79).

ARTHRITIS.—The predominant involvement of the hip, knee and ankle illustrates the importance of trauma secondary to weight-bearing as a predisposing factor in the localization of joint infection in brucellosis. The joint involvement is like that of most forms of septic arthritis, including those due to the pneumococcus, staphylococcus and streptococcus. The onset is abrupt and brings severe pain and swelling of the joint as well as purulent fluid from which Brucellae are readily cultured. When the hip is affected in children the apparent paresis due to pain and muscle spasm may bring an incorrect diagnosis of poliomyelitis, while the painful red swelling of the knee or ankle is sometimes mistaken for rheumatic fever.

Suppurative arthritis due to Brucella is much less common than arthralgia in brucellosis and should not be confused with it. The distinction between the two is important because arthralgia does not apparently result from actual infection of the joint; it seems related instead to the systemic effects of Brucella endotoxin and can be reproduced by injecting that substance intravenously. Both conditions must also be differentiated from the sterile hydrarthrosis described by Hughes (42) and Debono (20) in many patients with melitensis infections.

ENDOCARDITIS.—Except for the etiology, endocarditis in brucel-

losis is substantially the same as that caused by Streptococcus viridans. For this reason, the possibility of Brucella endocarditis must be considered in any patient who has clinical signs of bacterial endocarditis but whose blood is sterile by ordinary cultural technics. Both Str. viridans and Brucella attack chiefly the mitral and aortic valves, but prior disease of the valvular leaflet, while common, is not apparently a prerequisite for localization of Brucella as it usually is for streptococci (21, 64, 69, 86). The myocardial and renal lesions of streptococcal endocarditis are also found in Brucella endocarditis (86). In the myocardium a cellular reaction develops which is characterized by diffuse and focal mononuclear infiltrations, some of which are said to have the appearance of Aschoff lesions. In the kidney there is a diffuse glomerulonephritis for which embolization does not seem to be responsible. It is accompanied by swelling of the glomerular basement membrane and infiltration of glomeruli by mononuclear leukocytes. Infarcts appear in the spleen and other organs and passive congestion of the lung and liver results from heart failure.

An important feature in the fatal cases of endocarditis has been the almost universal absence of granulomas in the tissues (86, 87). The delayed type of dermal hypersensitivity to the Brucella cells or their protein fractions is also absent, although an immediate reaction can be elicited with their carbohydrate derivative (23). The absence of granulomas in biopsied hepatic tissue and bone marrow, or of hypersensitivity to Brucella antigens in a patient with serologic or bacteriologic evidence of brucellosis should thus bring to mind the diagnosis of endocarditis and lead to a careful examination for cardiac murmurs and embolic manifestations.

MENINGO-ENCEPHALITIS.—Brucellosis is the cause of a chronic infection of the central nervous system which has many features of tuberculosis and especially cryptococcal meningitis. In all 3 forms of meningitis there is a diffuse infiltration of the meninges with a plastic exudate which is mainly granulomatous in form and tends to involve blood vessels. This process is accompanied clinically by headache, focal neurologic signs and a spinal fluid pattern showing increased mononuclear cells and protein, with a lowered or normal sugar. In brucellosis the chief focal neurologic changes have consisted of 8th nerve injury with resultant deafness, tinnitus and ataxia. In addition there are regularly recurring

attacks of sensory and motor aphasia, paralysis or hemianesthesia which seem to arise from spasm, thrombosis or rupture of involved vessels (34, 83). Despite these extensive neurologic abnormalities, the course of this disease, like that of cryptococcal meningitis, may be remarkably benign with prolonged periods of remission and even recovery. Patients with active Brucella meningitis may be afebrile, ambulatory and even working at a time when their spinal fluid contains abnormal numbers of cells, protein and sugar. Although 13 verified cases have been reported in the literature, only 3 were fatal and complete autopsy findings were documented in but 1 (22, 34, 65). This patient died from rupture of a mycotic aneurysm of the basilar artery 13 months after onset of symptoms (34). There was thickening of the leptomeninges due to a chronic inflammatory process, and a heavy infiltration of the adventitia of the meningeal vessels. In the brain, collars of lymphocytes surrounded many blood vessels and inflammatory cells were present in the perineurium of the nerve roots. Br. suis was isolated from grayish-white "tubercules" in the leptomeninges overlying the superior surfaces of the cerebral hemispheres, and from a large blood clot involving the base of the brain.

Orchitis.—The incidence of this complication varies from 2.8% in abortus infections to 4 or 5% in melitensis and suis infections. In Spink's (79) series, involvement of the testicle appeared in 3 of 108 men from whom Br. abortus was isolated, while Hughes (42) described an incidence of 4 or 5% in Malta, and Hardy (35) noted its occurrence in 5% of male patients in Iowa, most of whom presumably had infections due to Br. suis. Testicular pain and swelling may appear alone or with epididymitis at the onset of brucellosis, in the midst of the course or during convalescence. Unilateral nonsuppurative inflammation is the rule, but it can extend to the other testicle (79). The orchitis eventually subsides in about 2 weeks, although a few cases persist for a much longer period.

SPECIAL FEATURES OF EACH TYPE OF BRUCELLOSIS
(see also table)

Melitensis Infections

Although infections due to Br. melitensis are not frequent in the United States, they are a serious, if not the chief, cause of

ESSENTIAL DIFFERENCES AMONG THE THREE TYPES OF BRUCELLOSIS

ETIOLOGY	CHIEF ANIMAL RESERVOIR	MODE OF INFECTION	GEOGRAPHIC DISTRIBUTION	RELATIVE SEVERITY OF ILLNESS	UNDULATION OF FEVER CURVE	UNIQUE CLINICO-PATHOLOGIC FEATURES	NEED FOR CO_2 IN BLOOD CULTURES	APPROXIMATE RELAPSE RATE AFTER THERAPY WITH TETRACYCLINE
Br. abortus	Cow	Eating dairy products; milking cows; butchering cattle; handling aborted fetuses	World-wide	Mildest	No*	None	Yes	30%
Br. suis	Pig	Butchering swine	North and South America only	Intermediate	Unusual	Calcified nodules in lung and spleen	No	60%
Br. melitensis	Goat, sheep	Eating dairy products (esp. cheese); milking goats	World-wide	Severest	Common	Neuritis; hydrarthrosis; pneumonia	No	60%

* Undulating fever reported in abortus infections in England by Dalrymple-Champneys (18).

brucellosis in many subtropical areas of the world. This disease is prevalent in goats in Mexico, France, Italy, Spain, Yugoslavia, Turkey, Israel and Egypt (60, 71). From these animals it is spread to man through eating cheese, milk and ice cream or, during milking, by contamination of the exterior of the body with large numbers of Br. melitensis in the milk, urine or feces. Because Brucella organisms are also present in dust, soil and agricultural plants in regions inhabited by infected animals, persons who never eat the milk or cheese of goats may nevertheless acquire caprine brucellosis. The marked invasiveness of Br. melitensis enables it to penetrate intact mucous membrances and skin. Cheese seems to enhance this invasiveness because it is sticky and remains in the mouth for a longer time than milk. Victims who are infected by eating cheese are thus denied the possible protective action of their gastric juice against Brucella organisms (30).

The great invasiveness of Br. melitensis also seems to account for the higher incidence of childhood brucellosis due to that species than to Br. abortus or Br. suis. According to Debono (20), brucellosis in Malta is commonest in children under 5 years of age, while in the United States brucellosis occurs least often in that age group. A high frequency in children is to be expected because milk forms the principal food in their diet, and the rare occurrence of childhood brucellosis in the United States is attributed to greater natural resistance to the infection among younger persons (53). Despite the high frequency of childhood brucellosis in Malta, this natural resistance in youngsters is evidenced by the very mild illness which characterizes brucellosis in Maltese children (20). In a certain sense the ability of Br. melitensis to establish infection in the resistant child is a fortunate epidemiologic accident because it probably immunizes against the severe form of brucellosis seen in the less resistant British adults in Malta during the 19th century (42).

Dairy products from sheep are another important source of human Br. melitensis infections and there is definite proof that the infection has spread to cows (59). In the United States, however, most human melitensis infections in recent years have occurred in packinghouse workers or farmers in Iowa and Minnesota and have been traced to direct contact with fresh pork or

the genital discharges of aborting sows (45). Because Br. melitensis was originally confined to the goat-raising areas of Texas, Arizona and New Mexico, it is likely that the disease was imported from the Southwest to Iowa.

Observations throughout the world during the past 70 years have clearly established that Br. melitensis is the cause of more severe illness than the other 2 species of Brucella. The malignant syndromes described by Hughes (42) in Malta in 1897 have been repeatedly observed in later years by Cantaloube (12) in France, Ruiz-Castaneda (15) in Mexico and Debono (20) in Malta. In their most violent form, melitensis infections may erupt suddenly with overwhelming, sustained hyperpyrexia, intense toxemia and death within a few days or weeks. In other cases, the course may be benign for a variable period and suddenly become malignant.

This syndrome is fortunately much less common than the undulant type of disease, which is also found exclusively in melitensis infections. The word "undulant" was first used extensively, in 1897, by Hughes (42), who was struck by the way in which the curves on the fever chart "undulate across the paper in waves of varying size." He regarded the undulating fever as the outstanding clinical feature of the infection and observed that it was a unique characteristic not present in other febrile diseases. For this reason he advocated the name "undulant fever" for the infection due to Br. melitensis. His suggestion has been justified in subsequent years by the fact that the undulant type of case remains the most frequent one in Malta and is regarded there as typical of brucellosis. The name is not suitable for the abortus or suis type of human brucellosis, however, because undulating fever curves are not ordinarily seen in those infections.

The duration of the individual waves varies from several days to a month, with an average of 2 weeks. The total number of waves is also variable from case to case; there may be as many as a dozen, but in most cases there are only 3 or 4. Each succeeding wave of fever tends to be shorter than the preceding one and brings with it a return of symptoms in a somewhat less severe form.

In addition to the malignant or undulant fevers, melitensis infections exhibit the ordinary intermittent fever curve of most febrile diseases. Any of these febrile types may be accompanied

by certain localizing manifestations; those which tend to be more characteristic of melitensis infections than the other forms of brucellosis are as follows.

PNEUMONIA.—Symptoms of respiratory tract disease are more frequent in melitensis than in suis or abortus infections (20, 42). Many patients have persistent coughs, bronchitis and bronchopneumonia, while lobar pneumonia is observed less often. The special tendency for pneumonia to occur in melitensis infections was recently illustrated in the United States by a study of 20 cases of bacteremic brucellosis at the Mayo Clinic. Pneumonia or pneumonitis was found in 3 patients with infections due to Br. melitensis, but in none from whom Br. suis or Br. abortus was isolated (38). The exact etiology of those pulmonary complications is obscure because repeated attempts to recover Brucella from the sputum have failed (20). It is possible that Brucella organisms do not enter the sputum because they are confined within the lymphatic structures of the respiratory tract, the alveolar septa or both. The absence of the organisms from the sputum could also be explained if the pulmonary involvements were examples of an allergic pneumonitis of the type produced experimentally in animals hypersensitive to Brucellae (11). Finally, it must be considered that these pneumonias are not due to Br. melitensis infection at all, but are secondary infections resulting perhaps from aspiration of oral bacteria during extreme debility.

SYNOVITIS (HYDRARTHROSIS).—Patients with melitensis infections are predisposed to a peculiar form of joint involvement from which only sterile synovial fluid containing lymphocytes is obtained (20, 42). The onset may be acute and accompanied by sudden intense pain as well as rapid swelling of the joint, without redness. The joints of the knee and ankle are involved more often than those of the upper extremities. Both monoarticular and migratory attacks are common. After several days abnormal findings usually disappear but some patients experience recurrences for weeks. Hughes observed that the subacute joint effusions were most common after the fever subsided and that they often appeared as an early and chief symptom in mild cases. He compared the sterile joint effusions of brucellosis with those of gonorrhea.

NEURITIS.—Although vague aches and pains are common to all forms of brucellosis, neuralgic and neuritic pains are especially prominent in melitensis infections (15, 20, 42). Often a definite nerve is affected and the most serious and troublesome condition is that occurring when the sciatic is involved. In the acute stages intermittent pain shoots down the nerve especially after unfavorable movements. The nerve itself is tender to pressure and marked hyperesthesia appears over the skin of the leg. In severe cases atrophy or paralysis also develops but recovery ordinarily occurs after weeks or months.

BACILLURIA.—According to the original studies of Kennedy (49) in 1905, and those of Killough, Magill and Smith (50) in Egypt in 1951, approximately 50% of patients with melitensis infections excrete Brucellae in the urine at some stage in the active disease or convalescence. Urine cultures are only intermittently positive, however, and evidence of pyelonephritis or cystitis occurs only rarely. Hence, it would seem that the bacilli pass through the kidney without establishing serious local infection in most cases.

PURPURA HEMORRHAGICA.—This is an uncommon but serious complication of brucellosis and probably a result of hypersplenism and thrombocytopenia. It is completely reversible with tetracycline therapy (82).

ABORTION.—Severe melitensis infections often produce human abortion, especially if hyperpyrexia is marked and sustained (20).

BRUCELLOSIS DUE TO BR. SUIS

This form of human brucellosis is a disease of the Americas and generally limited to the hog-raising areas of the middle western United States, Brazil and Argentina (35, 56). Danish hogs are also infected by a variety of Br. suis, but this organism is not capable of producing human brucellosis (79). Suis infections are typically acquired as an occupational disease by farmers, butchers, or packinghouse workers after direct contact with the tissues of infected hogs. Br. suis is, however, a serious potential public health menace to consumers of dairy products because cattle sometimes become infected by association with hogs. When this occurs the more invasive suis organisms establish

a much higher incidence of clinical infection than that following the distribution of Br. abortus in raw milk and outbreaks of epidemic proportion may occur among customers of the involved dairy (5, 8, 27, 46). Fortunately, pasteurization is a widely practiced safeguard which can prevent such accidents; but the hazard of individual infection through immediate exposure to infected animals is an almost insoluble epidemiologic problem. The reason is that brucellosis may be impossible to recognize by ordinary methods in a hog (43). While it is true that in certain herds the high incidence of abortion, lameness and orchitis may call attention to the disease, there are many herds of swine in which abnormalities are almost never apparent. Even abortion may occur so early in the course of swine pregnancy that it is unnoticed. Equally troublesome in this regard is the fact that as many as 41% of infected hogs may fail to develop a significant titer of agglutinins in their blood. These unnoticed infections may then be spread about the premises from ruptured abscesses or in the urogenital discharges and milk of infected sows which farrow normally. Because Br. suis can survive at various environmental temperatures for weeks in water, soil and hog excreta, personal hygiene and environmental sanitation are of the greatest importance in the prevention of human infections due to Br. suis. It would be essential, of course, to eradicate brucellosis in swine before its spread to humans could be prevented, but the necessary measures are so drastic that universal cooperation may be impossible to secure. Whole herds need to be tested for agglutinins to detect infection and the whole herd destroyed to insure elimination of every infected animal.

Among hogs developing pathologic changes, the outstanding lesions are encapsulated abscesses in the vertebrae, extremities and viscera. The abscesses are basically suppurative granulomatous lesions in which multinucleated giant cells and calcified foci may be prominent (28, 51). The suppurating properties of Br. suis are also observed in both human and experimental infections. In guinea pigs all strains of Br. suis may be expected to produce numerous abscesses while only a few strains of Br. melitensis and an exceedingly rare strain of Br. abortus may do so (9).

In human infections due to Br. suis, abscesses are especially likely to develop in the bones, joints, lung and kidney but have

also been reported in the liver, lymph nodes and spleen. Their manifestations are described in the following paragraphs.

OSTEOMYELITIS.—In addition to the lesions already described in the vertebrae, osteomyelitis may be present in the long bones, ilium and scapula. These destructive abscesses may involve multiple areas in a given bone and more than one bone in the same patient (51). Although the osteomyelitis itself is circumscribed, the abscesses will rupture into the soft tissue and through the skin to create extensive sinuses from which cheesy material and sequesters of bone may drain for months or years. These sinuses may appear in the axillary, gluteal, sacral and inguinal regions as well as the areas adjacent to abscesses of long bones (51, 79).

PULMONARY NODULES.—In contrast to the acute pneumonias of melitensis infections, the pulmonary lesions from which Br. suis have been isolated are well-defined nodules occurring in the midpulmonary or mediastinal areas of patients who have no systemic symptoms of brucellosis (92). On surgical removal these have been shown to be granulomas composed of firm but friable caseous material enclosed within a shell of vascularized connective tissue. The granulomatous character of the lesion is apparent from the layer of epithelioid cells located between the cheesy center and fibrous wall. Although Brucellae can be recovered in culture, they cannot be seen in stained sections, nor can the granulomas be identified when compared histologically with those of tuberculosis and fungous diseases of the lung (92).

These granulomas present the same clinical problem as other pulmonary coin lesions observed on roentgenogram and must be resected surgically before they can be distinguished from cancer of the lung. The clinical history may resemble that of bronchogenic carcinoma even to the extent that hoarseness may result from the adherence of a diseased tracheobronchial lymph node to the recurrent laryngeal nerves. In the experience of Weed and associates (92), bacteriologic examination of the sputum or bronchial washings is valueless and the agglutination test is not positive in significant titer in patients with nodular pulmonary brucellosis.

PYELONEPHRITIS.—Br. suis is an important cause of that type of nephrocalcinosis which is associated with chronic pyelonephritis. In general, when nephrocalcinosis accompanies pyelone-

phritis the etiologic organism is a urea-splitter which establishes a chronic, relatively mild but persistent renal infection. The ammonia released from the urea into the tubules or interstitial tissue of the kidney is thought to raise the pH until the alkalinity permits precipitation of calcium salts by decreasing their solubility (58). Because Br. suis is capable of releasing ammonia by hydrolysis of urea, it is possible that the urease factor is an important determinant in the pathogenesis of renal calcification. Of probably greater significance, however, is the peculiar tendency for the caseating abscesses of suis infections to undergo calcification in all tissues regardless of whether a high urea concentration exists as it does in the renal tubules (10, 51).

Because of the renal calcification, pyelonephritis due to Br. suis also resembles renal tuberculosis. In both conditions there is marked pyuria accompanied by sterile urine when cultures are performed without regard for the special requirements of the etiologic organisms (1). Moreover, if the renal tissues are examined after surgical removal or biopsy, the two conditions cannot be distinguished on the basis of morphology alone; in both tuberculosis and brucellosis the involved kidney contains numerous granulomatous lesions with central caseation and multinucleated giant cells (1). Sometimes the two diseases can be distinguished by the routine agglutination test for brucellosis, but agglutinins may be absent in suis pyelonephritis as they are in other forms of chronic suppurative infections due to Br. suis (91). Since the usual systemic manifestations may also be absent, the only dependable diagnostic procedure is cultural isolation of the etiologic agent.

LYMPHATIC, SPLENIC AND HEPATIC SUPPURATION.—These reticulo-endothelial organs are sometimes the seat of severe focal areas of caseation from which Br. suis can be isolated. In both peripheral lymph nodes and spleen the findings of calcified areas of caseous necrosis have resulted in an incorrect initial diagnosis of tuberculosis in patients whose positive agglutination tests ultimately led to successful attempts at cultural isolation of Br. suis from the infected tissues (16, 17). The lesions which have been described in the spleen are laminated nodules of fibrous tissue and calcium (16). These calcifications are prominent on roentgenograms of the abdomen and must therefore be distinguished

from such other causes of splenic calcification as tuberculosis and histoplasmosis. In 2 reported cases, serum agglutinins were markedly elevated in contrast to other forms of focal suppurative suis infections (16, 61). It is also of interest that, on physical examination, the spleens of these 2 patients were found to be huge. Splenectomy revealed that one weighed 2,000 Gm. and the other over 1,200 Gm. The larger spleen was apparently responsible for thrombocytopenia which disappeared after splenectomy (61).

Brucellosis Due to Br. Abortus

This is the most widespread form of human brucellosis in the United States and Great Britain but fortunately the mildest. Man gets the disease from infected cattle by drinking milk and by direct exposure to infected animals. Of these 2 routes of dissemination the second is more important as a cause of clinical brucellosis. Br. abortus invades the tissues of many persons who drink contaminated raw milk, but only a low percentage of these develop symptomatic evidence of infection. Numerous members of a large family may be infected after drinking milk from a herd of cattle with brucellosis and only one may become ill (73). The evidence for infection in these asymptomatic persons consists of dermal hypersensitivity to Brucella antigens, positive agglutination tests and in rare cases positive blood cultures. The low rate of clinical disease is explained by the relatively low virulence of Br. abortus as compared to Br. suis and Br. melitensis (9). An interesting and revealing source of data on the comparative virulence of the 3 species is brought out by an analysis of 38 Brucella infections among laboratory workers (55). Although most cultures handled by laboratory workers are presumably Br. abortus, only 1 worker was infected by that species while Br. melitensis was isolated from 21 and Br. suis from 12.

In addition to the low virulence of Br. abortus, the dangers of drinking milk contaminated by that organism are minimized by 3 other factors. (1) The bactericidal action of gastric juice (30), (2) the dilution of milk from infected cows by milk from numerous noninfected cows when the supplies from different animals are mixed at the dairy before the raw milk is marketed. The im-

portance of dilution is emphasized by the occurrence of epidemic brucellosis due to Br. abortus only in those rare instances in which raw milk has been distributed to numerous consumers from a single infected source (89), (3) the natural resistance to brucellosis of children, the chief consumers of milk (20, 79).

In the light of these considerations, it is not surprising that only 25% of abortus infections can be attributed to drinking raw milk (53). Most infections are acquired by persons whose occupations involve contact with infected cattle. Because the genital discharges during abortion, as well as the blood, viscera and udder of the cow may all be infected with Br. abortus, there are several modes of contact, involving various occupations, that can result in human infection. Many patients are packinghouse workers who work on the "beef-kill" and become splattered with infected blood and body fluids while slaughtering livestock. A high incidence of infection is also found among veterinarians and results from their handling the fetus and membranes of aborting heifers. A third important occupational hazard is dairy work, and especially milking, because the skin becomes heavily contaminated with milk during the stage of its great infectivity. In addition to immediate exposure to infected cattle, farm personnel undoubtedly acquire abortus infections through contact with materials in the barns, pastures and feed lots, which become contaminated during lactation, abortion or in the postpartum period.

These occupational hazards are reflected in the high incidence of abortus infections in men. The epidemiologic survey of Magoffin and Spink (53) in Minnesota revealed that approximately 70% of abortus infections were in adult males between the ages of 20 and 55 and that most gave a history of contact with infected animals. Occasionally the patient's history indicated that hogs, rather than cattle, may have been the sole possible source of infection. Such cases, taken together with the findings of Br. abortus in tissues of swine, provide definite proof that the hog may also serve as an occasional reservoir of human infection (59). Spread of Br. abortus to swine is probably the consequence of their close association with cattle on feed lots. It has been suggested that passage through the pig could render Br. abortus more virulent for man.

In addition to their exposure to naturally occurring abortus infections in livestock, veterinarians are likely to be infected with the artificially attenuated strain "19" (75). This strain of Br. abortus is used as an effective vaccine for immunizing calves against brucellosis and protects against moderate exposure for at least 2 to 3 years. The living but attenuated vaccine is not entirely innocuous and may not only produce abortion occasionally in adult cows, but can also establish clinical brucellosis in man. It is important to point out, however, that the bovine and human disease due to strain 19 never occurs except after artificial inoculation (79). In the case of the veterinarian such inoculation is, of course, accidental and, despite the tremendous number of bacilli which may be introduced, the resulting clinical illness is no more severe than the naturally acquired disease. Two clinical syndromes may occur in these self-inoculated veterinarians. One is no different from the usual clinical form of brucellosis and symptoms appear after an incubation period of about a week; the other is characterized by an incubation period of only 6 hours, intense local inflammation at the point of inoculation and severe systemic symptoms of fever and chills. The second type of illness is believed to result from hypersensitivity to Brucella antigens even though the patient has been previously immunized by repeated low-grade infections from infected cattle. The repeated exposures are themselves characterized by a similar reaction in which a rash appears on the arms after contact with the blood from cows with brucellosis (79).

These exceptional accidents with strain 19 are so infrequent and so easily avoided with due care that they cannot be regarded as a serious objection to the use of the vaccine in controlling brucellosis. Because Brucella infection in a cow can be recognized reliably by the blood agglutination test, the reactors can be slaughtered and the calves protected by vaccination with strain 19. In this way considerable progress can be made in controlling the animal reservoir of human abortus infections (79).

Except for these epidemiologic considerations, there is nothing unique about human abortus infections that enables the clinician to distinguish its symptoms or physical findings from those of the other 2 varieties of brucellosis. The fever curves of abortus infections are no different from those of most infectious diseases

and its complications (spondylitis, arthritis, endocarditis and meningo-encephalitis) are equally characteristic of the melitensis and suis varieties of brucellosis. While it is true that infections due to Br. abortus are milder and less resistant to treatment, this fact is only of statistical importance and not of value in recognizing the individual case.

LABORATORY DIAGNOSIS

Culture

The most important procedure in the diagnosis of brucellosis is recovery of the bacillus in culture. Brucellae are usually recovered from the blood but occasionally from urine, joint fluid, spinal fluid or pus aspirated from focal abscesses. They are more difficult to isolate from these sources, however, than such common pathogenic bacteria as the pneumococcus, staphylococcus, streptococcus or colon bacillus. This fact is not surprising in view of the exceptional growth requirements of all Brucella organisms, as well as their relatively low concentration in the blood and other infected fluids (40). The bacteremia of brucellosis, especially in abortus infections, does not appear to be sustained as it is, for example, in staphylococcal septicemias, so that only one of several samples of blood may yield Brucellae.

Although no media have been devised which permit Brucellae to grow as rapidly or profusely as the common pyogenic cocci or coliform bacilli, there are available commercially several excellent media which can be depended upon for recovering the organism in many cases of brucellosis. These include Tryptose Broth (Difco Laboratories), Trypticase Soy Broth (Baltimore Biological Laboratories) and Albimi Brucella Broth (Albimi Laboratories). They are distributed in dehydrated form by the manufacturers and must be reconstituted before use. In many places the liquid medium is dispensed with 1% citrate in sealed 3-oz. bottles, and the blood or other body fluid is introduced by inserting the needle of the syringe through the sterilized rubber stopper. This technic is not only more convenient than the use of cotton-stoppered flasks, but also avoids the introduction of air contaminants due to opening the flask. The stoppered bottle is especially useful in the isolation of Br. abortus because it retains

CO_2 in the concentration of 10% usually required for growth of that species when freshly isolated (40). Br. melitensis and Br. suis can be cultured without added CO_2 but, in a patient suspected of brucellosis, it is often impossible to predict which species is responsible. If facilities are not available for preparing sealed bottles containing CO_2, they can be purchased. The commercial bottles (B-D Vacutainer) contain Trypticase Soy Broth and have been found to be reliable for culturing Brucella from patients. Partial evacuation of the bottle by the manufacturer enables blood to be obtained without a syringe by means of a rubber tubing with needles at each end for puncturing both vein and rubber stopper.

These bottles can be improved even further by the ingenious device of Ruiz-Castaneda (14), who introduced a layer of agar against one wall. The agar seems to be of value in separating Brucella cells from growth-suppressive factors in the blood (40). It has been suggested that leukocytes stick to the agar surface and that the intracellular organisms can then develop into colonies as the phagocyte disintegrates. Whether or not this explanation is valid, it is a fact that colonies of Brucella appear on the agar within a week, while contaminants are noted in 48 hours or less, a period too short for Brucella to develop on first isolation. The appearance of typical Brucella colonies on the agar alerts the person handling the culture to the need for proper care in subsequent work with this dangerous micro-organism.

While these media offer the best available growth conditions for Brucellae, their value is limited because of the small numbers of bacteria which must establish growth under the adverse conditions of an artificial environment. An obvious means of increasing the bacterial inoculum is to culture large volumes of blood by resorting to repeated cultures over several days. This method provides a better opportunity for securing samples during periods of transient increase in the degree of bacteremia than would be the case if an equal total volume were to be collected at one time.

Brucellae may be cultured from the urine, in addition to the blood, of many patients with infections due to Br. melitensis (49, 50). While urine cultures are less commonly positive in these patients than blood cultures during the acute stage of the disease, Brucellae persist longer in the urine during the latter stages of

the infection (49). For this reason urine cultures are more important than blood cultures in assessing the bacteriologic results of treatment during the period when melitensis infections have recovered symptomatically. Except for melitensis infections, however, there is no point in culturing urine routinely and, unless localizing complications are present, there is little to be gained by culturing other materials than blood. Because of variation in the number of cultures attempted and differences in degree of bacteremia, the rate of recovery of the organism has varied from 40 to 80% in clinically active cases. Brucella has occasionally been isolated from the bone marrow in uncomplicated infections when the blood cultures were negative (79). In the presence of suppurating lesions of bones, soft tissues or joints, there is little difficulty in obtaining the organism by culturing the purulent specimen. Isolation of Brucella from the spinal fluid of patients with neurologic lesions, however, may be difficult. Because Brucella is highly virulent for the chick embryo, fertilized hens' eggs may be used successfully for recovering the organism from spinal fluid in cases of meningitis (83). To overcome the limitations of a small bacterial inoculum, it is probably wise to collect 30–40 ml. of spinal fluid by means of a single lumbar puncture and to use the centrifuged sediment for inoculation of the egg.

Agglutination Test

In the absence of a positive culture, the agglutination test with blood serum assumes great importance in the diagnosis of brucellosis. The test must be done carefully with well-standardized antigens, however, to be of real value to the clinician. Recently the Committee on Brucellosis of the National Research Council recommended the use of antigens prepared according to the criteria of the Bureau of Animal Industry and the recommendation has been accepted by the laboratories of many state health departments (70). When such an antigen is properly used, almost every patient with active brucellosis, regardless of infecting species, will be found to have a high titer of agglutinins in his serum. A titer of less than 1:100 almost always means that active brucellosis is absent, while a higher titer is compatible with the possibility that the patient's symptoms are those of brucellosis.

In over 90% of patients the titer can be expected to exceed 1:320, and in that range or higher it is of great significance even when obtained on a single specimen of blood (53). In other words, it is not necessary to demonstrate a rising titer because the agglutinins have often reached their height by the time the physician first examines the patient.

Unlike a positive blood culture, however, a positive agglutination test even in high titer does not establish a diagnosis of brucellosis. In several conditions without active Brucella infection, agglutinin titers higher than 1:100 may be present. Perhaps the most common circumstance of this type is found in the person who has recovered from clinical or subclinical brucellosis. High titers without infection are also encountered in persons who have been subjected to skin tests, or who have been treated without justification by the intramuscular administration of Brucella filtrates. Because of the antigenic relationships between Brucella and the cholera vibrio, immunization with cholera vaccine also produces high titers of Brucella agglutinins (24). In service-men given such vaccination there may be positive agglutination tests for Brucella in titers as high as 1:2,560. A similar antigenic relationship exists with Pasteurella tularensis, but the titer of Brucella agglutinins is usually too low to offer diagnostic difficulties in tularemia (79).

Skin Test

The routine use of intradermal Brucella antigens has no place in the diagnosis of brucellosis. A positive reaction will occur in a person who has been previously exposed to Brucella organisms and it does not depend on active infection at the time of the test. The skin test has a special usefulness in Brucella endocarditis, the only form of brucellosis giving a negative intradermal reaction in the presence of high agglutinin titers (23, 86); a negative test is also useful in evaluating the agglutinin response after cholera vaccination because Brucella hypersensitivity does not accompany the formation of Brucella agglutinins in these circumstances (24). In all other instances the information obtained from skin testing adds nothing to that provided by the more informative agglutination test. The Brucella skin test does not,

therefore, compare in importance with the tuberculin test, which retains a certain utility in the absence of a dependable serologic test in tuberculosis.

Other Tests

Opsonocytophagic index.—The test for opsonins measures the capacity of a serum to enhance the phagocytosis of Brucella organisms by blood leukocytes. According to Huddleson (41) and Harris (37) the opsonocytophagic power of blood gives an index of the activity of infection when examined in conjunction with the skin test and agglutination test. For example, low opsonic activity in the presence of positive agglutination tests is said to be diagnostic of active infection. Other investigators have found, however, that the opsonocytophagic index is not as informative as the agglutination test (79). It is difficult to perform in comparison with the agglutination test and dangerous to laboratory workers because living bacteria are customarily used. For these reasons most laboratories have discontinued its use and rely on the technically simple agglutination test.

Complement-fixation test.—This test has not been evaluated extensively, but the limited experience of those who have used it indicates that it is more complicated but not more informative than the agglutination test (79).

Blood count.—The presence of marked leukocytosis weighs against the diagnosis of brucellosis. In 90% of patients the total leukocyte count is normal or reduced and lymphocytes are usually relatively increased in number. The lymphocytes also undergo a change in morphology so that numerous forms resembling those of infectious mononucleosis are sometimes present, but the serum titer of sheep cell agglutinins after absorption with guinea-pig kidney is not elevated significantly in brucellosis (79). Anemia is not to be expected as it is in other infections which continue for several weeks or months (33).

Sedimentation rate.—It is important to recognize that the sedimentation rate of the blood is normal in nearly 50% of patients with brucellosis (3). A normal rate, therefore, is of diagnostic significance in distinguishing brucellosis from those generalized infections in which the speed of sedimentation is in-

variably increased. The test is also useful for following the activity of brucellosis in the remaining 50% whose blood sedimentation is rapid at the time of initial examination.

TREATMENT

Theoretical Basis

Of several antibiotics used in the treatment of human infections, only streptomycin kills Brucella organisms in broth cultures when the drugs are used in concentrations possible to achieve clinically in the blood of patients. The tetracycline drugs (oxytetracycline, chlortetracycline and tetracycline) and chloramphenicol, on the other hand, are only inhibitory in these concentrations, and penicillin usually allows unrestricted growth (94). In infected chick embryos, however, no antibiotics, including streptomycin, eradicate Brucella organisms from the tissues when given in doses which provide concentrations equal to those in the blood of patients (66). This paradox seems to be explained by the observations that Brucellae proliferate intracellularly and that intracellular forms are then protected from streptomycin as well as from the tetracyclines and chloramphenicol (31, 54). Elimination of the organisms from the tissues is not a prerequisite, however, for protection of experimentally infected animals from the lethal and suppurative effects of Brucellae. Chlortetracycline, for example, produces only a modest reduction in the number of bacteria in the spleens of animals with brucellosis yet dramatically prevents death by all 3 species, reduces by half the size of the spleen in abortus infections, and almost eliminates the extensive suppurative lesions due to Br. suis in guinea pigs (79). A further decrease in the number of bacteria in the spleen can be induced by the additional use of streptomycin in the chlortetracycline treated animals. Moreover, in animals which possess well-advanced granulomatous reactions to aid the antibiotics, the tissues are actually sterilized under the influence of such combined therapy (79). The combination of streptomycin and chlortetracycline can be shown to have a greater activity against Brucellae when used together than would be expected from their individual antibrucella action and they are said, therefore, to be synergistic. A similar synergism results from the combined use of streptomycin and sulfadiazine (67).

The prevention of death in animals despite the persistence of large numbers of Brucellae in the tissues suggests that the tetracyclines and other antibiotics prevent the elaboration of lethal toxins by inhibiting bacterial multiplication. While antibiotics are thus able to counter what appear to be the toxic effects of living bacteria, they do not prevent purified Brucella endotoxins from killing experimental animals (72). In order to achieve such protection it is necessary to administer cortisone rather than antibiotics.

Treatment of Clinical Brucellosis

The action of antibiotics in human brucellosis is similar in many respects to that observed in experimental animals. The tetracycline drugs, for example, produce dramatic improvement in every case of brucellosis, but the organisms frequently persist in the tissues and induce exacerbations in 30–60% of those patients given one course of treatment. The highest rate of permanent recovery has been reported in abortus infections. Seventy per cent of patients infected with Br. abortus remain well after approximately 2 weeks of treatment with oral chlortetracycline given in divided doses totaling 2.0 Gm. daily and 90% are permanently recovered after a second course of this treatment (79). In suis and melitensis infection, the excellent immediate response is followed in about 60% of patients by clinical or bacteriologic recurrences, occurring mainly during the second or third week after completion of tetracycline therapy (19, 50, 57). The relapses tend to be less severe than the initial attacks and usually cease recurring after 1 or 2 subsequent trials of the drug. The total dose seems to be an important factor in determining permanent remission as indicated by the results of Janbon and Bertrand (44), who reported lasting recovery in 85% of patients with melitensis infection given 4.0 Gm. of chlortetracycline daily for 1 month.

These results in Brucella infections treated with chlortetracycline are similar to those obtained with combined streptomycin-sulfadiazine therapy (23). The drugs have usually been administered in doses of 1.0 Gm. streptomycin twice daily for 7 to 14 days and 1.0 Gm. sulfadiazine 4 times daily for 21 days. While they are curative in many cases, including patients with such

serious complications as bacterial endocarditis, they have been replaced by the tetracyclines because streptomycin is less convenient to administer, produces 8th nerve toxicity, and induces slower clinical improvement. If streptomycin is used it is generally given in combination with one of the tetracyclines. Several reports describing excellent results in brucellosis suggest that the synergism in experimental studies may also operate clinically in patients given both streptomycin and one of the tetracyclines (38, 39). The usual dose of streptomycin is 0.5 Gm. twice daily intramuscularly and that of the tetracycline 0.5 Gm. 4 times daily orally. Streptomycin should never be used by itself, however, because it appears to be ineffective in human brucellosis unless given jointly with a sulfonamide or tetracycline drug (63).

While these advances in antibiotic therapy of brucellosis have relieved the sufferings of many patients with brucellosis, there is still need for even more effective measures. An ingenious and highly promising innovation has been recently advanced by Ruiz-Castaneda (13), who treated 68 patients infected by Br. melitensis with intramuscular injections of amphoteric oxytetracycline in amounts not larger than 160 mg. per week. The aim of this unusual procedure was to provide insoluble particles of oxytetracycline so that they could be picked up by phagocytes and thus have access to the intracellular Brucellae. Ruiz-Castaneda contends that the high relapse rate in brucellosis represents a failure of soluble antibiotics to penetrate the cell membrane of parasitized phagocytes. He further suggests that the neutrophilic leukocytes carrying the particles of antibiotics are eventually phagocytosed by reticulo-endothelial cells harboring Brucellae. The striking abolition of bacteremia in his patients receiving relatively minute doses of oxytetracycline strongly supports the theoretical basis of this treatment and warrants confirmatory trials by others.

The only other antibiotic of definite value in brucellosis is chloramphenicol (50, 93). It does not seem to bring about the prompt recovery in abortus infections that is regularly observed with the tetracyclines, but the 2 are said to be equally effective in melitensis infections. Because severe marrow depression is a serious possibility in patients given chloramphenicol, this drug should not be given routinely in the treatment of brucellosis.

In addition to the antibiotics, the adrenal hormones have exhibited a clinical effectiveness which might have been predicted from their experimental action against Brucella endotoxin. Both cortisone and ACTH bring about recovery in acutely febrile patients even more rapidly than the tetracyclines. With tetracyclines alone the temperature remains elevated for about 4 days in acute infections, and in almost 50% of patients the fever is intensified during the first 24 or 48 hours. Sometimes this aggravation of fever is accompanied by vascular collapse, presumably due to the excessive release of endotoxin from the numerous bacilli destroyed by the antibiotics (82). The addition of streptomycin does not shorten the febrile period, but ACTH or cortisone, when given with these antibiotics, terminates the fever in less than a day and suppresses the Herxheimer-like febrile exacerbations (52, 85). This symptomatic improvement with ACTH has also been reported in the absence of covering antibiotic therapy and was followed by complete recovery of the patient. There seems to be every reason, therefore, to give adrenal hormone therapy in conjunction with effective antibiotics to severely ill patients with brucellosis and especially those in whom a Herxheimer-like exacerbation might be disastrous. The hormone need be used for only a few days until symptomatic improvement occurs. ACTH in divided doses of 100 mg. daily intramuscularly would be effective and not lead to the adrenal suppression reported after administration of cortisone. Moreover, short-term steroid therapy in these doses is not accompanied by the other dangers sometimes occurring with chronic use of adrenal hormones in massive doses.

The antibiotic therapy described is not only effective in the ordinary case of brucellosis but is usually curative in patients with serious complications. There have been excellent results in the treatment of spondylitis, arthritis, severe purpura, meningitis, pneumonia and bacterial endocarditis (23, 38, 82, 83). The marked tendency for new bone formation makes surgery unnecessary in the treatment of spondylitis in brucellosis. Surgery must sometimes be used in brucellosis, however, in conjunction with antibiotics for the drainage of suppurative foci, the removal of enormous spleens which are overly destructive of the blood elements, the removal of pulmonary "coin" lesions due to Br. suis,

and perhaps for the removal of pyelonephritic kidneys when the process is unilateral and hopelessly destructive.

A final therapeutic measure of importance in brucellosis is reassurance. The prolonged illness often shakes the emotional stability of patients who cannot easily regain their normal energy and ambition. Physicians who fail to recognize that the symptoms are those of convalescence rather than active infection sometimes initiate further treatment with antibiotics and vaccines. The ineffectiveness of these measures in relieving the weakness may lead to discouragement and even hopelessness, so that many are driven into a state of chronic emotional invalidism. The most important treatment during convalescence is for the physician to convey to the patient the conviction that he is on the road to full recovery. He should be encouraged and even urged to resume his usual activities and to overcome his inclination to remain inactive.

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